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Alacrima as a Harbinger of Adrenal Insufficiency in a Child with Allgrove (AAA) Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 6
Final Diagnosis: Allgrove syndrome
Symptoms: Achalasia • adrenal insufficiency • alacrima
Medication: —
Clinical Procedure: —
Specialty: Pediatrics and Neonatology

Objective: Rare disease

Background: Allgrove syndrome, or triple "A" syndrome (3A syndrome), is a rare autosomal recessive syndrome with variable phenotype, and an estimated prevalence of 1 per 1,000,000 individuals. Patients usually display the triad of achalasia, alacrima, and adrenocorticotropin (ACTH) insensitive adrenal insufficiency, though the presentation is inconsistent.

Case Report: Here, the authors report a case of Allgrove syndrome in a pediatric patient with delayed diagnosis in order to raise awareness of this potentially fatal disease as a differential diagnosis of alacrima.

Conclusions: The prevalence of Allgrove syndrome may be much higher as a result of underdiagnosis and missed diagnosis due to the variable presentation and sudden unexplained childhood death from adrenal crisis. The authors review the characteristic symptoms of Allgrove syndrome in relation to the case study in order to avoid missed or delayed diagnosis, potentially decreasing morbidity, and mortality in those affected by this disease.

MeSH Keywords: Adrenal Insufficiency • Endocrinology • Esophageal Achalasia • Hospitals, Pediatric

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Background

Caused by mutation of the AAAS gene on chromosome 12q13, Allgrove syndrome, or 3A syndrome, is a rare autosomal recessive endocrine and neurologic disorder with an estimated prevalence of 1 per 1,000,000 individuals. Patients usually display the triad of achalasia, alacrima, and adrenocorticotropic (ACTH) insensitive adrenal insufficiency, while 60% may also have autonomic dysfunction [1]. Onset typically occurs by age 10 years; however, new-onset diagnoses have been reported into adulthood [2]. A complete triad increases diagnostic specificity, while severity of symptom manifestations aids in diagnosis.

In this case report the authors discuss a 6-year-old female of Jamaican descent with nonconsanguineous parents who presented with adrenal crisis. Unrecognized by the patient's pediatrician and specialists alike, she began displaying syndrome-specific symptoms at the age of 2 years. Initially, this involved decreased tear production and motor weakness. Three years later she began showing signs of achalasia, diagnosed as gastroesophageal reflux (GER). These symptoms were not correlated with a possible diagnosis of Allgrove syndrome until age 7, after presenting with adrenal crisis.

Case Report

A 6-year-old female presented to the Emergency Department (ED) with the complaint of diffuse intermittent abdominal pain, vomiting, fatigue, and fever. The abdominal pain and weakness were gradually worsening for 2 weeks prior to presenting to the ED. The patient's past medical history was pertinent for a presumed diagnosis of gastroesophageal reflux at the age of 5 years. Leading to this diagnosis was the complaint of stomach problems, mostly consisting of food becoming "stuck" when she swallowed. Her mother reported she also had frequent falling bouts while walking, worsening over the past year, with her balance becoming more unsteady as the day progressed. A pediatric neurologist assessed her 3 months prior to presentation; however, no diagnosis was made.

Vital signs in the ED consisted of a temperature of 103.6°F, blood pressure 91/48, and heart rate of 135 beats per minute. Noted on physical examination were gingival hypertrophy, and hyperpigmentation of the buccal mucosa and gingiva. Growth parameters consisted of weight and height in the 79th and 96th percentiles, respectively. Complete blood count was unremarkable, with urinalysis suggestive of a urinary tract infection, for which treatment with intravenous Ceftriaxone (50 mg/kg/day) was initiated. Her basal metabolic panel was significant for sodium of 132 mmol/L, chloride of 102 units, bicarbonate of 19 units, and anion gap of 11. She was admitted

to the pediatric inpatient floor, where she continued to receive Ceftriaxone and 6% correction fluids.

During admission, additional laboratory results included an ACTH level of 617 pg/mL (normal 9–57 pg/mL) and a low morning cortisol level of 0.77 ug/dL (normal 6–28 ug/dL). ACTH stimulation was performed with 0-minute results of 0.87 ug/dL (normal >5 ug/dl) and 60-minute result of 0.34 ug/dL (normal 18–20 ug/dl). Thyroid function tests showed an elevated thyroid-stimulating hormone of 5.77 mIU/mL (normal 2.7–4.2 mIU/mL) and a normal total thyroxine of 7.3 ug/dL. Thyroglobulin antibodies and thyroid peroxidase antibodies were both negative. In summary, her symptoms and lab results were consistent with adrenal insufficiency. The patient was placed on hydrocortisone (5 mg 3 times daily), with substantial improvement of weakness and of stomach pain. She did not require additional fludrocortisone replacement therapy because her electrolytes had normalized after the completion of correction fluids and the initiation of hydrocortisone therapy.

It was not until after this admission at 7 years of age that she was diagnosed with Allgrove syndrome. During an endocrinology outpatient visit, her mother mentioned that the patient began using lubricating eye drops at the age of 4 years. When asked about this in detail, she stated that at 2 years of age the patient stopped having overflow tears. While this information was brought to the attention of the pediatrician at the time, no intervention was recommended. For this reason the mother thought a lack of tear production could be normal and did not reveal the information whenever questioned regarding the patient's past medical history. With the addition of this missing piece to the puzzle, a presumptive diagnosis of Allgrove syndrome was made.

Genetic testing (GeneDx) was performed via genomic DNA PCR-amplification and bidirectional sequencing of exons 1-16 with flanking splice sites. This revealed 2 heterozygous disease-causing mutations in the 3A syndrome gene, consistent with Allgrove syndrome (Table 1).

After the diagnosis of Allgrove syndrome was made, both parents were offered genetic testing, but they declined. They also denied knowledge of other family members being affected by Allgrove syndrome. In regards to continued management, this patient is being followed by a pediatric endocrinologist for monitoring of electrolytes and maintenance of hydrocortisone therapy (5 mg 3 times a day). Due to complications of achalasia, she underwent surgical correction via a Heller myotomy at the age of 10 years old, with significant improvement of symptoms. In addition to using lubricating eye drops as needed, she continues to see an ophthalmologist yearly in order to monitor alacrima.

Table 1. Genetic mutations identified via GeneDx testing.

Mutation	Mutation effect	Mutation prediction
c.57_58delTG	Two-base deletion causing a frameshift and changing the tyrosine 19 codon to a premature stop codon	Loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay
c.526dupC	Cytosine base duplication causing a frameshift starting with codon arginine 176, changing this amino acid to a proline residue and creates a premature stop codon at position 4 of the new reading frame	Loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay

Discussion

In 3A syndrome, approximately 90% of mutations involve altered genetic modification, leading to a repeat of the AAAS gene on chromosome 12q13, [3] encoding the ALADIN nuclear pore complex protein [2]. Clinical manifestations may be due to a deficiency or misplacement of the protein into the cytoplasm or nucleus causing increased sensitivity of the 3A patient's adrenal and neuronal fibroblasts to oxidative stressors [2].

Alacrima is considered to be an early symptom of Allgrove syndrome, and may appear during early infancy [4]. In accordance with previous literature, the initial manifestation of 3A in this patient was decreased tear production. Had alacrima been a focus earlier, perhaps her emergent adrenal crisis could have been avoided, as her adrenal status would have been monitored over time. This oversight has occurred in many of the reported cases of 3A syndrome. As such, we would like to stress the importance of routinely inquiring about tear production in order to diagnose and properly manage these complex patients.

Esophageal achalasia in pediatrics is rare, with less than 5% of patients presenting under the age of 15 years [5]. Achalasia in Allgrove syndrome typically presents with vomiting (84.6%), dysphagia (69.2%), weight loss (46.0%), and chronic cough (46.1%) [5]. Often misdiagnosed as gastroesophageal reflux, achalasia should be considered as a differential in GERD unresponsive to treatment.

Sixty percent of 3A patients also have comorbid neurodegenerative processes, most frequently consisting of mild intellectual disability [2]. The neurologic disabilities described in 3A may include severe motor, sensory, and autonomic impairment. Due to the complication of optic atrophy in the Allgrove population, patients should be examined yearly by ophthalmology.

Adrenal crisis is the primary cause of mortality in those with Allgrove syndrome. Adrenal insufficiency results from a progressive disorder and tends to present with episodic attacks of hypoglycemia and progressive hyperpigmentation [3]. The

mechanism by which adrenal insufficiency occurs in patients with Allgrove syndrome is thought to be a result of the ALADIN gene. The AAAS gene product is the nuclear pore complex protein alacrima-achalasia-adrenal insufficiency neurological disorder (ALADIN), which plays a role in redox homeostasis in human adrenal cells and inhibits steroidogenesis [2]. Currently, there is no protocol for patients diagnosed with Allgrove syndrome who not have experienced adrenal insufficiency. However, we recommend close monitoring of serum electrolytes, especially during episodes of acute illness, in order to prevent adrenal crisis. Hydrocortisone, possessing both glucocorticoid and mineralocorticoid properties, is the treatment of choice in patients with adrenal insufficiency.

With an autosomal recessive mode of inheritance, there is a 25% recurrence risk in future pregnancies. Identification of the mutation(s) allows for prenatal diagnosis by chorionic villus sampling or amniocentesis, as well as preimplantation diagnosis. DNA confirmation in the proband also allows for early identification of currently asymptomatic siblings at risk in order to provide proper monitoring.

Conclusions

Although Allgrove syndrome is thought to affect 1 in 1,000,000 individuals, the prevalence may be much higher due to underdiagnosis and missed diagnosis caused by the variable presentation and sudden unexplained childhood death from adrenal crisis. Since alacrima is a rare finding that may only present with conjunctival injection and irritation, tear production should be a routine question in the pediatric office. If it is deficient, we emphasize that other clinical features associated with Allgrove syndrome should be investigated in order to avoid potentially fatal consequences. As noted in this case, there were multiple pertinent findings that could have led to the suspicion of 3A; however, the timing of these revelations and evolution of symptom development over several years contributed to the delayed diagnosis.

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